alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl;

(b) separating and purifying the product of step (a);

(c) reacting the product of step (b) with a second monomer N^2, a dimer N^2-N^3 or a trimer N^2-N^3-N^4; and

(d) repeating steps (b) and (c) to produce an LPC-bound biopolymer having m monomers, where m is 3 to 100, wherein:

N^1, N^2, N^3...N^m are biopolymer monomers;

the dimers and trimers comprise the monomers; and

the protocol used in steps (c) and (d) to synthesize the biopolymer is the phosphoramidite protocol.

REMARKS

A check in the amount of $180 for a Supplemental Information Disclosure Statement is enclosed. Any fees that may be due in connection with the filing of this paper, if the attached check is in the wrong amount, improper or is missing, or with this application during its entire pendency, may be charged to Deposit Account No. 50-1213. If a Petition for an Extension of Time is required, this paper is to be considered such petition.

Claims 6, 7, 17, 20, 21, 29, 31, 39, 40 and 47-49 are pending following the entry of this amendment. Claims 9-11, 14-16, 22, 25, 26, 32 and 45,

which are directed to the subject matter withdrawn from the instant application, are cancelled herein without prejudice or disclaimer. Applicant reserves the right to file divisional and continuation applications directed to any cancelled subject matter.

Claims 6, 7, 17, 31, 39, 40 and 48 are amended herein. Basis for the amendments to the claims can be found in the claims as originally filed and in the specification. In particular, the addition of the proviso to claim 6 finds basis in the specification, on page 7, line 12-14, and page 20, lines 27-29, which recite that:

> In other more preferred embodiments, the LPCs are chosen with the proviso that Z contains at least one, preferably at least two, more preferably at least three **or more** phenylene or alkylene units.

Thus, the amendment has basis in the specification and no new matter has been added.

A Supplemental Information Disclosure Statement also accompanies this Amendment.

REJECTION OF CLAIMS UNDER 35 U.S.C. §112, FIRST PARAGRAPH: WRITTEN DESCRIPTION REJECTION

Claims 6, 7, 17, 20, 21, 29, 39, 40 and 47-49

Claims 6, 7, 17, 20, 21, 29, 39, 40 and 47-49 are rejected under 35 U.S.C. §112 as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed subject matter. It is noted in the Office Action that the specification presents the particular compounds 1,3,5-tris(2,5-diaza-9-(5'-O-(4,4'-dimethoxytriphenyl-methyl)-2'-deoxythymidine-3'-O-yl)-1,6,9-troxononyl)-benzene and 1,3,5-tris(9-(2'-deoxy-thymidine-3'-O-yl)-2,5-diaza-1,6,9-troxononyl)-benzene, as well as their preparation. The Office Action alleges that these compounds do not constitute the compounds within the general definition

of formula (Id) and the disclosure of their preparation does not contitute adequate written disclosure for how to make instant LPCs of formula (Id). The Office Action urges that the data presented shows the synthesis of the phenyl trisubstituted with a diamide from a phenyl triester, which allegedly is not adequately correlative to the elected species of a phenyl trisubstitued with an alkyl or phenyl group as is broadly claimed. The Office Action further urges that an adequate representation of species requires that the species that are expressly described be representative of the entire genus and what constitutes a "representative number" is an inverse function of the predictability of the art. The Office Action further alleges that a skilled artisan would not recognize that a compound capable of being synthesized via standard carbonyl chemistry would be representative of compounds incapable of being synthesized in a similar manner. It is further urged that a skilled artisan would not recognize that a diamide compound would be representative in function to the alkyl, phenyl, alkylphenyl, or phenylalkyl compound as brodly claimed. The Office Action concludes that there is no data to support applicant's claim that at the time of filing, the compounds of the invention were made and used by minor modification to the protocol developed for the diamide compounds. Applicant respectfully traverses the rejection.

Relevant Law

The purpose behind written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description, has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

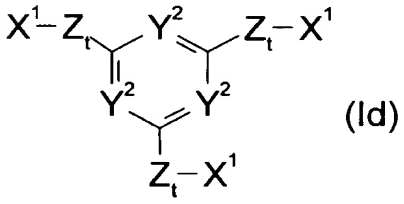
An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a

description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Instant claims 6, 7, 17, 20, 21, 29 and 49

Instant claim 6 is directed to a liquid phase carrier (LPC) of formula (Id):



(Id)

wherein Z is any combination of 1-12 units selected from 1,4-phenylene and methylene units, which units may be combined in any order, with the proviso that if Z is methylene, then Z contains more than three methylene units and the remaining variables are as defined therein.

Claims 7, 17, 20 and 21 further define the variables in claim 6.

Claim 29 is directed to the LPC of claim 6 coupled to a photocleavable linker.

Claim 49 is directed to the LPC of claim 6 coupled to a biopolymer.

Analysis

First, applicant respectfully submits that the Office Action has raised several points in support of the written description rejection. Careful review of the arguments reveals that many of the issues raised are directed towards an enablement rejection rather than the written description. Nonetheless, applicant has provided rebuttal to the arguments in the Office Action in the "Rebuttal to the Arguments in the Office Action" section of this response.

Second, applying the guidelines for a written description analysis of claims directed to a genus reveals that the written description requirement is satisfied. The analysis for compliance with the written description requirement for the claims directed to a genus is as follows:

a) does the art indicate substantial variation among the species within the genus?

b) are there a representative number of examples explicitly or implicitly disclosed in the application as determined by assessing whether the skilled artisan would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species?

In this instance the answer to each of a) and b) is yes.

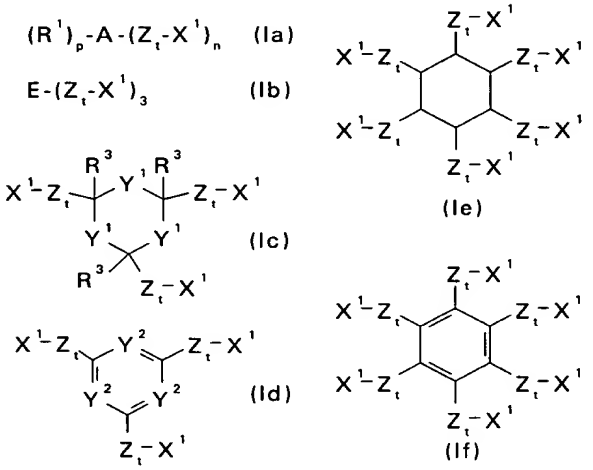
a) There is no indication in the art that there is substantial variation among members of the genus. All the LPCs within the scope of the instant claims have a benzene ring as a central core and symmetrically substituted methylene or phenylene units or any combination thereof with reactive groups that are used in biopolymer synthesis at the end. The instant claims and the specification as originally filed, explicitly disclose the structure of the instantly claimed LPCs. The reactive groups used in biopolymer synthesis are disclosed in the application and several references are cited wherein the reactive groups are disclosed. The application discloses that all the LPCs within the scope of the instant claims have similar functional features. Further, as

discussed in detail below those skilled in the art recognize that the instantly claimed LPCs can be prepared by slight modification of known reaction protocols.

b) The specification explicitly describes preparation of 1,3,5-tris(2,5-diaza-9-(5'-O-(4,4'-dimethoxytriphenyl-methyl)-2'-deoxythymidine-3'-O-yl)-1,6,9-troxononyl)-benzene and 1,3,5-tris(9-(2'-deoxy-thymidine-3'-O-yl)-2,5-diaza-1,6,9-troxononyl)-benzene which represent LPCs with common structural features; namely, a benzene ring with symmetrically substituted reactive groups that are used in biopolymer synthesis. Therefore, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant had possession of the genus as claimed. Thus, the application complies with the written description requirement for the claims directed to a genus by meeting the requisite criterion.

Further, applicant respectfully submits that the application discloses the instantly claimed LPCs, for example, see specification page 3, line 3 through page 4, line 8, which recite:

In one embodiment, the LPCs have one of formulae (I):



where Sp is $(R^1)_p$-A, E or a cyclic group (i.e. heterocycles, carbocycles, aryls, heteroaryls, such that the resulting structure is symmetrically disposed around the center of the cyclic group) with the linked "Z_t" moieties, where t is 0 or 1. As depicted the cyclic and aromatic rings have 6 members; it is understood that fewer or higher-number membered rings may also be used, as long as the resulting structure possesses the requisite symmetry, and the number of linkages for synthesis of the biopolymers is greater than two.

The instantly claimed LPCs of formula (Id) are also disclosed on page 19, lines 4-35 and claim 5 as originally filed. The application describes all the components of the claimed LPCs. For example, Z is described on page 4, lines 11-22 as:

Z, where t is 0 or 1, is a divalent hydrocarbon, containing one or more or mixtures of phenylene or alkylene groups, and contains a sufficient number of carbons (0, where t is 0, up to as many as 24 or more) to prevent or to reduce interactions among the chains in each biopolymer during synthesis. Preferably Z, typically containing from 1 up to 30 carbons or more, is any combination alkylene and arylene units, preferably methylene and phenylene units, preferably 1-12, more preferably 2-12, particularly 3-12, more particularly 4-12, most preferably 6-12, 7-12 or 8-12 units, preferably selected from 1,2-, 1,3- or 1,4-, preferably 1,4-, phenylene and alkylene units, more preferably methylene units, which units may be combined in any order;

The specification on page 19, lines 24-28 discloses:

Z is a divalent hydrocarbon as described above, and is preferably any combination of 0-12, preferably 1-12, more preferably 2-12, particularly 3-12, more particularly 4-12, most preferably 6-12, 7-12 or 8-12 units in which each unit is preferably selected from 1,4-phenylene and methylene, which units may be combined in any order;

X is described in the specification on page 4, lines 22-27 as:

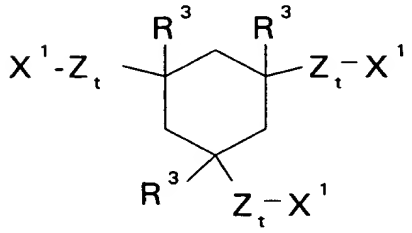
X^1 is any reactive group that is used in biopolymer synthesis (see, e.g., U.S. Patent No. 5,198,540, the disclosure of which is incorporated herein by reference), and is preferably halide, OH, SH, NH_2, COR^5 or $COOR^4$; n is preferably 3 or 4; R^4 is selected from hydrogen, alkyl, aryl, aralkyl,

heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl; R^5 is halide, heteroaryl or pseudohalide;

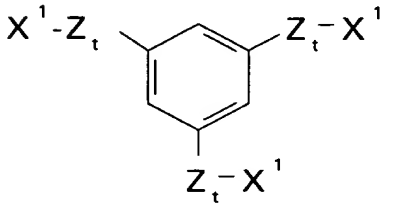
X is further disclosed in the specification on page 19, lines 29-34, and claims 4, 5, 6, 14, 15 and 16. Y^2 is disclosed on page 19, lines 34-35 , as being selected from CH and N and t is disclosed, for example, on page 19, line 29 as equal to 0 or 1.

The LPCs of formula (IId) as claimed in claim 17 are disclosed in the specification on page 24, lines 6-33 and in claim 17 as:

In more preferred embodiments, the LPCs have formulae (IIc) or (IId):



(IIc)



(IId)

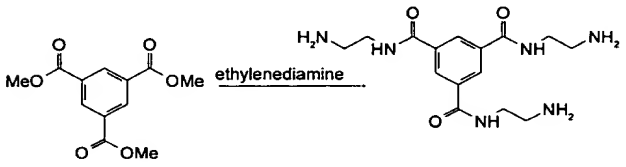
where Z is any combination alkylene and phenylene units, of 0-12 units, preferably 1-12, more preferably 2-12, particularly 3-12, more particularly 4-12, most preferably 6-12, 7-12 or 8-12 units, preferably selected from 1,4-phenylene and methylene, which units may be combined in any order; t is 0 or 1; X^1 is any reactive group which can be used in biopolymer synthesis (see, e.g., U.S. Patent No. 5,198,540, the disclosure of which is incorporated herein by reference), and is preferably halide, OH, SH, NH_2, COR^5 or $COOR^4$; n is 3 or 4; R^4 is selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl; and R^5 is halide, heteroaryl or pseudohalide.

The LPCs of instant claim 31 are described in the application on page 42 and claims 31 and 32 as originally filed. Furthur, the application exemplifies the

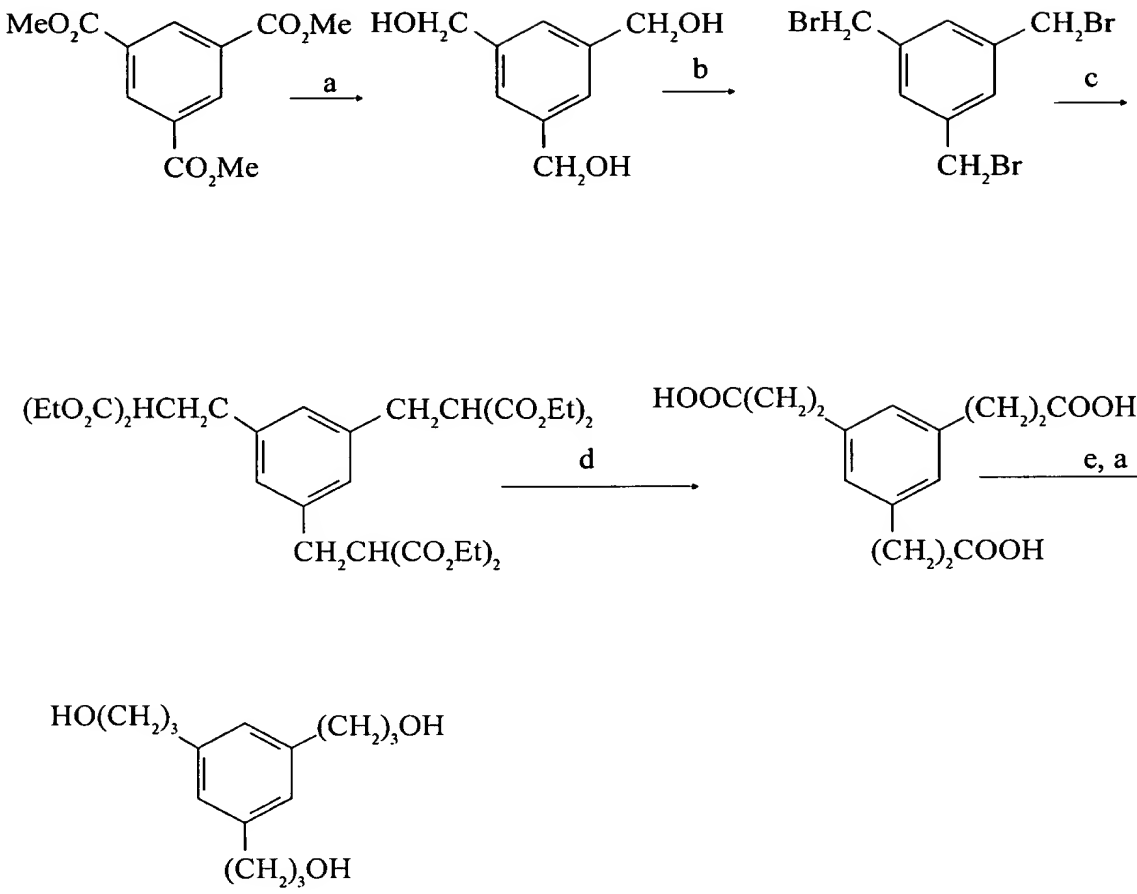
LPCs on pages 57-60, in example 4. The LPC of instant claim 49 is described in claim 49 as originally filed.

Thus, the instantly claimed LPCs are explicitly disclosed in the application as originally filed. The Examiner is reminded that possession does not mean physical possession but appreciation. It is not necessary to make and test all or any embodiments to meet the written description requirement.

Furthermore, the application demonstrates the protocol for the preparation of an exemplary LPC, 1,3,5-benzene tricarboxylic acid tris-N-(2-aminoethyl)amide, starting from commercially available 1,3,5-benzene tricarboxylic acid trimethyl ester using ethylenediamine as follows:



A skilled artisan would recognize, based on the application disclosure above, that by choosing appropriate starting materials and modification to the protocol disclosed in the application, the LPCs of the instant claims can be easily synthesized. For example, a skilled artisan would recognize that the LPCs within the scope of the instant claims, when Z is 3-12 or 4-12 methylene units and X is COOH or OH can be prepared by starting with benzene tricarboxylic acid trimethyl ester and performing routine sequence of reactions known in the art. Such reactions are disclosed by, for example, Yamagiwa *et al.* in Bull. Chem. Soc. Jpn. **69**, 3317-3323 (1996) for the preparation of 1,3,5-tris(2-carboxyethyl)benzene and 1,3,5-tris(3-hydroxypropyl)benzene from 1,3,5-benzene tricarboxylic acid trimethyl ester as reproduced below:



a) $LiAlH_4$, THF, r.t., 1.5 h; b) HBr, AcOH, reflux, 1 h; c) $CH_2(CO_2Et)_2$, NaH, THF, r.t., 2h d) (i) KOH, H_2O, reflux, 16h; (ii) 180°C, 3h; e) MeOH, cat., H_2SO_4, reflux, 24 h

The reaction protocols reported in the literature can be modified by a skilled artisan to arrive at the LPCs within the scope of the instant claims.

Further, Bradshaw *et al.* (J. Org. Chem. **58**, 7694-99 (**1993**)) have reported preparation of 1,3,5-tris(2-hydroxymethyl)benzene. The reaction protocol described therein can be modified to arrive at the LPCs within the scope of the instant claims by a skilled artisan.

Preparation of various symmetrically trisubstituted benene derivatives is also recorded by Cochrane *et al.* in *J. Chem Soc.(C)*, 630, **1968**.

Therefore a person of skill in the art would recognize that the LPCs within the scope of the instant claims wherein Z is 1-12, 3-12 and 4-12 methylene units can be prepared by choosing appropriate starting materials and slight modification to the protocol disclosed in the application. With little experimentation, a skilled artisan would be able to modify the reactions reported in the literature, to prepare other starting materials suitable for the preparation of the LPCs of the instant claims wherein Z is any combination of 1-12 units selected from 1,4-phenylene and methylene units.

It is not necessary to include in the specification that which those of skill in the art know. The specification is presumed to include all such knowledge. Thus the application as originally filed discloses the instantly claimed LPCs and describes an exemplary reaction protocol that can be modified by a skilled artisan to arrive at the LPCs of the instant claims. In light of the foregoing, the present application clearly conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the presently claimed subject matter. Specifically, it is clear from the disclosure that the claimed LPCs can be obtained by choosing appropriate starting materials and modifying the protocol disclosed in the application.

Claims 39, 40, 47 and 48: Claims directed to method of solution phase biopolymer synthesis

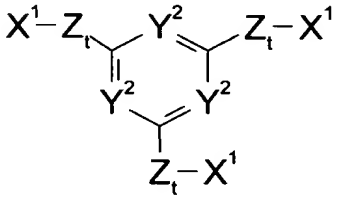
Claims 39, 40, 47 and 48 are rejected under 35 U.S.C. §112 for lack of written description. The Office Action alleges that the specification does not have enough support for the claims to the method of solution phase biopolymer synthesis using the LPCs of formula (Id). Applicant respectfully disagrees.

Relevant Law

As discussed above.

Instant claims 39, 40, 47 and 48

Independent claim 39 and independent claim 48 are directed to a method of solution phase biopolymer synthesis using an LPC of formula (Id),



(Id)

wherein Z is any combination of 0-12 units selected from 1,4-phenylene and methylene, which units may be combined in any order; t is 0 or 1 and the other variables are as defined therein. Claim 40 further defines the LPCs and claim 47 further defines the monomers used in the method of claim 39.

Analysis

The method of solution phase biopolymer synthesis as claimed in instant claims 39 and 48 for the LPC of formula (Id) where t=0, is described in the application on page 8, lines 7-24; page 44, lines 4-21, and claims 33 and 38 as originally filed. The method of biopolymer synthesis as claimed in instant claim 39 is exemplified in example 7 for the synthesis of d(5'-O-DMT-$G^{ib}pA^{bz}pC^{bz}pG^{ib}pG^{ib}pC^{bz}pC^{bz}pA^{bz}pG^{ib}pT)_3$-Aryl-LPC. As discussed above, based on the application disclosure and information available in the art, a skilled artisan can further choose appropriate starting materials and modifications to the protocol disclosed in the application to arrive at other LPCs within the scope of formula (Id) with little experimentation. The method for biopolymer synthesis described in detail in the application allows a skilled artisan to apply the method to other LPCs within the scope of the instant claim.

Therefore, the specification provides adequate written description for the method of biopolymer synthesis using LPCs of formula (Id) and there is no basis to conclude that applicant was not in possession of the claimed subject matter.

REBUTTAL TO THE ARGUMENTS IN THE OFFICE ACTION

Applicant herein provides response to the specific issues raised in the Office action.

Lack of Adequate disclosure

The Office Action alleges that the disclosure of the preparation of compounds 1,3,5-tris(2,5-diaza-9-(5'-O-(4,4'-dimethoxytriphenyl-methyl)-2'-deoxythymidine-3'-O-yl)-1,6,9-troxononyl)-benzene and 1,3,5-tris(9-(2'-deoxy-thymidine-3'-O-yl)-2,5-diaza-1,6,9-troxononyl)-benzene in the application does not constitute adequate written disclosure for **how to make LPCs of formula (Id)**.

Applicant respectfully submits that **description of how to make the instantly claimed LPCs is irrelevant for written description requirement**. To satisfy the written description requirement, a specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. As discussed above, in the instant case the LPCs of formula (Id) are explicitly disclosed and various components thereof are described in the application on pages 3, 19, 25-26, and 42, as originally filed and provide adequate written description.

Furthermore, the application discloses preparation of an exemplary LPC starting from a commercially available compound 1,3,5-benzene tricarboxylic acid trimethyl ester by demonstrating the steps involved in the preparation thereof. As discussed above, a skilled artisan with the information available in the art and based on his/her knowledge, can make modifications to the disclosed reaction protocol to arrive at the LPCs of formula (Id) as instantly

claimed. Therefore, the disclosure in the application enables a person of skill in the art to make the instantly claimed LPCs. Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. It would be unfair and unduly limiting to require applicant to limit the claims to the exemplified species when the specification clearly places those of skill in the art in possession of a larger genus of the LPCs as instantly claimed. Therefore, it would be unfair, unduly limiting and contrary to the public policy upon which the U.S. patent laws are based to require applicant to limit the claims only to the exemplified species:

See, e.g., In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts".
>
> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require applicant to limit the claims to only the exemplified species would permit those of skill in the art to practice what is disclosed in the application, but avoid infringing such limited claims. One of skill in the art could readily modify the exemplified LPCs disclosed in the application as taught in the specification. The first paragraph of §112 requires only that the disclosure be sufficient to teach one of skill in the art how to make and use the claimed subject matter without undue experimentation. As discussed above, the specification discloses the LPCs and describes various components thereof in

detail. Based upon the disclosure those skilled in the art can make and use the LPCs as claimed.

Further, a patentee not only is entitled to narrow claims particularly directed to a specific embodiment, but also to broad claims that define an invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). As discussed above, applicant has described the LPCs and provided an exemplary protocol to make certain LPCs. Based on this disclosure, a person of skill in the art can make LPCs within the scope of instant claims.

Predictability in the art

The Office Action urges that there is no predictability established in the art with respect to synthesizing phenyl trisubstituted alkyl, phenyl, alkylphenyl or phenylalkyl based on the synthesis of a phenyl trisubstituted with a diamide.

As discussed above, the synthesis of instantly claimed LPCs can be achieved by using appropriate starting materials and by modifications to the protocol disclosed in the application. For example, phenyl trisubstituted compounds reported in the art or can be prepared by a skilled artisan with little experimentation from the knowledge available in the art, can be used for the preparation of the instantly claimed LPCs using routine modifications to the protocol disclosed in the application. As evidenced by the articles discussed above, such reactions have well established predictability in the art. The question of predictability in the art for synthesizing phenyl trisubstituted alkyl, phenyl, alkylphenyl or phenylalkyl based on the synthesis of a phenyl trisubstituted with a diamide is irrelevant because a person of skill in the art would recognize that the instantly claimed LPCs can be made with appropriate starting materials and modifications to the protocol disclosed in the application.

Methodology for carbon-carbon bond formation

The Office Action alleges that applicant would have to establish that the methodology for carbon-carbon bond formation is the same for attaching an alkyl or phenyl group to a phenyl as for attaching an amide.

As discussed above, a skilled artisan, based the information available in the art, would recognize that phenyl trisubstituted with alkyl or phenyl groups can be used as starting materials to arrive at instantly claimed LPCs with little experimentation. Therefore, there is no need to establish that the methodology for carbon-carbon bond formation is the same for attaching an alkyl or phenyl group to a phenyl as for attaching an amide.

Data presented in the application

The Office Action alleges that the data presented in the application shows the synthesis for the phenyl trisubstituted with a diamide from a phenyl triester, which is not seen to be adequately correlative for the elected species of a phenyl trisubstitued with an alkyl or phenyl group as is broadly claimed. The Office Action further urges that an adequate representation of species requires that the species that are expressly described be representative of the entire genus and what constitutes a "representative number" is an inverse function of the predictability of the art. The Office Action further alleges that a skilled artisan would not recognize that a compound capable of being synthesized via standard carbonyl chemistry would be representative of compounds incapable of being synthesized in a similar manner. It is further urged that a skilled artisan would not recognize that a diamide compound would be representative in function to the alkyl, phenyl, alkylphenyl, or phenylalkyl compound as brodly claimed.

As discussed above, the application discloses synthesis of 1,3,5-tris{2,5-diaza-9-(5'-O-(4,4'-dimethoxytriphenyl-methyl)-2'-deoxythymidine-3'-O-yl)-1,6,9-trioxononyl}-benzene ((DMT-dT)$_3$-Aryl-LPC) and 1,3,5-tris(9-(2'-deoxythymidin-3'-O-yl)-2,5-diaza-1,6,9-trioxononyl)-benzene (dT$_3$-Aryl-LPC). These LPCs and

the instantly claimed LPCs possess the common structural feature namely benzene ring symmetrically substitued with reactive groups used in biopolymer synthesis. Further, the LPCs of instant claims are explicitly disclosed in the application. Applicant respectfully submits that the reactions illustrated in the application demonstrating the preparation an exemplary LPC and its use in the biopolymer synthesis can easily extended by a skilled artisan for the preparation of LPCs within the scope of the instant claims based on the application disclosure and the information available in the art. Such reactions involve routine chemistry which has well established predictability in the art. Furthermore, there is no need to disclose any examples in the application to satisfy written description requirement and the applicant is entitled to claim routine modifications to the specific examples disclosed.

Compounds of instant claims

The Office Action concludes that there is no data to support applicant's claim that at the time of filing, the compounds of the instant claims were **made and used** by minor modification to the protocol developed for the diamide compounds.

Applicant respectfully submits that the Office Action is once again raising the issue of enablement in the written description rejection. The question of "make and use" is irrelevant in written description rejection. As stated in the Office Action, a written description analysis involves:

1) field of the invention and predictability of the art,

2) breadth of the claims, and

3) possession of the claimed invention at the time of filing for each claimed species/genus.

None of these factors require "make and use" aspect of the claimed subject matter. The Examiner is reminded that there is no requirement to prepare any or all embodiments of the claimed LPCs to satisfy written description requirement and examples are not required to satisfy written

description. The application as originally filed, discloses the instantly claimed LPCs and describes all the components thereof. Further, possession does not mean physical possession but appreciation. In light of the discussion presented above, the present application clearly conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the presently claimed subject matter. Specifically, it is clear from the disclosure that the claimed LPCs can be obtained by choosing appropriate starting materials and modifying the protocol disclosed in the application.

Use of instantly claimed LPCs

Applicant respectfully submits that the use of LPCs of formula (Id) in the method for biopolymer synthesis is described in detail in the application, for example in the specification on page 8, lines 7-24; page 44, lines 4-21, as originally filed. The method of biopolymer synthesis as claimed in instant claim 39 is exemplified in example 7 for the synthesis of d(5'-O-DMT-$G^{ib}\underline{p}A^{bz}\underline{p}C^{bz}\underline{p}G^{ib}\underline{p}G^{ib}\underline{p}C^{bz}\underline{p}C^{bz}\underline{p}A^{bz}\underline{p}G^{ib}\underline{p}T)_3$-Aryl-LPC. As discussed above, based on the application disclosure and information available in the art, a skilled artisan can further prepare other LPCs of formula (Id) for use in the method for biopolymer synthesis.

REJECTION OF CLAIMS 6, 7, 20, 39, 40 AND 47-49 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 6, 7, 20, 39, 40 and 47-49 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. Applicant respectfully traverses this rejection.

"pseudohalide"

Claims 6, 39 and 48 are rejected for reciting the term "pseudohalide". The Office Action alleges that in the absence of particular moieties that would be construed as pseudohalides or distinct language to describe the structural

features or the chemical names of the pseudohalides for use in the instant compounds, the identity of such groups would be difficult to describe.

Applicant respectfully submits that the term "pseudohalide" is defined in the specification, see, *e.g.*, page 12, lines 25-29 as follows:

> As used herein, pseudohalides are compounds that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides (X^-, in which X is a halogen, such as Cl or Br). Pseudohalides include, but are not limited to cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethyl and azide.

Thus, the term "pseudohalide" is clearly defined in the application and its use does not render claims 6 and 39 indefinite.

Claim 40: Antecedent basis

The Office Action alleges that claim 40 lacks antecedent basis for the recitation of 1,3,5-tris{2,5-diaza-9-[5'-O-(4,4'-dimethoxytriphenyl-methyl)-2'-deoxythymidine-3'-O-yl]-1,6,9-trioxononyl}-benzene and 1,3,5-tris[9-(2'-deoxythymidin-3'-O-yl)-2,5-diaza-1,6,9-trioxononyl]-benzene. The Office Action notes that claim 40 depends from independent claim 39. Independent claim 39 is allegedly limited to phenyl compounds trisubstituted with Z_t-X^1, wherein Z is 1-12 units of 1,4-phenylene or methylene groups, t is 1-12 and X^1 is OH, SH, NH_2, COR^5 or $COOR^4$. The Office Action urges that the above mentioned compounds are not within the scope of such limitation. Applicant disagree.

Applicant respectfully submits that claim 39 recites

> Z is any combination of **0-12** units selected from 1,4-phenylene and methylene, which units may be combined in any order; **t is 0 or 1**; X^1 is OH, SH, NH_2, COR^5 or $COOR^4$.

Thus, independent claim 39 is not limited to phenyl compounds trisubstituted with Z_t-X^1, wherein Z is 1-12 units of 1,4-phenylene or methylene groups, t is 1-12 and X^1 is OH, SH, NH_2, COR^5 or $COOR^4$. Therefore, claim 39 provides proper antecedent basis for recitation of 1,3,5-tris{2,5-diaza-9-[5'-O-(4,4'-dimethoxytriphenyl-methyl)-2'-deoxythymidine-3'-O-yl]-1,6,9-trioxononyl}-

benzene and 1,3,5-tris[9-(2'-deoxythymidin-3'-O-yl)-2,5-diaza-1,6,9-trioxononyl]-benzene.

Phosphoramidite protocol

The Office Action alleges that recitation of "phosphoramidite protocol" renders claim 48 indefinite. The Office Action alleges that it is unclear if the claim is limited to methods of solution phase synthesis of biopolymers comprising nucleotides.

Claim 48 is directed to a method of solution phase biopolymer synthesis, comprising the steps of

(a) reacting an LPC with a first monomer N^1; wherein the LPC has formula I(d), where the variables are as described therein,

(b) separating and purifying the product of step (a);

(c) reacting the product of step (b) with a second monomer N^2, a dimer N^2-N^3 or a trimer N^2-N^3-N^4; and

(d) repeating steps (b) and (c) to produce an LPC-bound biopolymer having m monomers, where m is 3 to 100, wherein:

N^1, N^2, N^3...N^m are biopolymer monomers;

the dimers and trimers comprise the monomers; and

the protocol used in steps (c) and (d) to synthesize the biopolymer is the phosphoramidite protocol.

Applicant respectfully submits that the claim is not limited to methods of solution phase synthesis of biopolymers comprising nucleotides because phosphoramidite protocol can be used in synthesis of biopolymers comprising monomers other than nucleotides. Therefore, a person of skill in the art would recognize that recitation of "phosphoramidite protocol" does not limit the claim to methods of solution phase synthesis of biopolymers comprising nucleotides.

Applicant respectfully requests reconsideration and withdrawal of this rejection.

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KÖSTER *et al.*	)
Serial No.:	09/484,484	)
Confirmation No.:	9747	)
Filed:	January 18, 2000	)
For:	*SOLUTION PHASE BIOPOLYMER SYNTHESIS*	)
Art Unit:	1623	)
Examiner:	Young, J.	)

ATTACHMENTS TO THE AMENDMENT

The following attachments are provided:

(1) Marked up paragraphs and claims in accordance with 37 CFR §1.121; and

(2) a Supplemental Information Disclosure Statement.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KÖSTER *et al.*	)
Serial No.:	09/484,484	)
Confirmation No.:	9747	)
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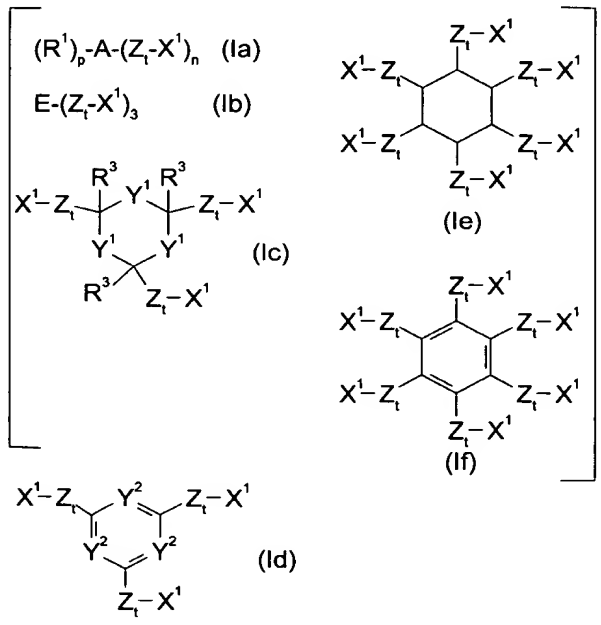
For:	*SOLUTION PHASE BIOPOLYMER SYNTHESIS*	)
Art Unit:	1623	)
Examiner:	Young, J.	)

MARKED UP CLAIMS (37 CFR §1.121)

Please amend claims 6, 7, 17, 31, 39, 40 and 48 as follows:

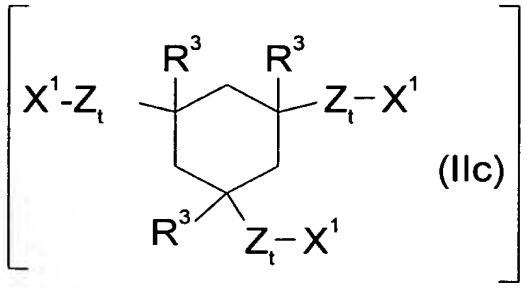
6. (Amended three times) A liquid phase carrier (LPC) that has [formulae (I)] <u>formula (Id)</u>:



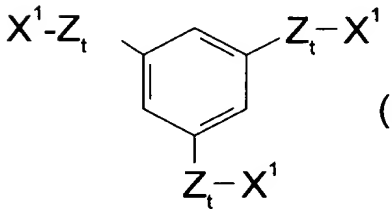
wherein: [A is silicon; E is nitrogen or P(O); R^1 and R^3 are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; p is 0 or 1;] Z is any combination of 1-12 units selected from 1,4-phenylene and methylene units, which units may be combined in any order[, with the proviso that if the LPC is of formula (Ia) or (Ib), then Z contains at least two phenylene or methylene units;] t is 1; X^1 is OH, SH, NH_2, COR^5 or $COOR^4$ where R^4 is selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl, and R^5 is halide, heteroaryl or pseudohalide; n is 3 or 4; <u>with the proviso that if Z is methylene, then Z contains more than three methylene units</u> ; [Y^1 is CH_2, NH, S or O;] Y^2 is [selected from] CH [and N]; [R^1, R^3,] X^1, [Y^1], Y^2 and Z are unsubstituted or substituted with one or more substituents each independently selected from Q; and Q is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl.

7. (Amended twice) The LPC of claim 6, wherein Z is a group with three or more points of attachment: one to [A, E, or] the cyclic nucleus, and the others to two or more X^1 groups.

17. (Amended twice) The LPC of claim 6, wherein the LPC has [formulae (IIc)] or] formula (IId):



(IIc)



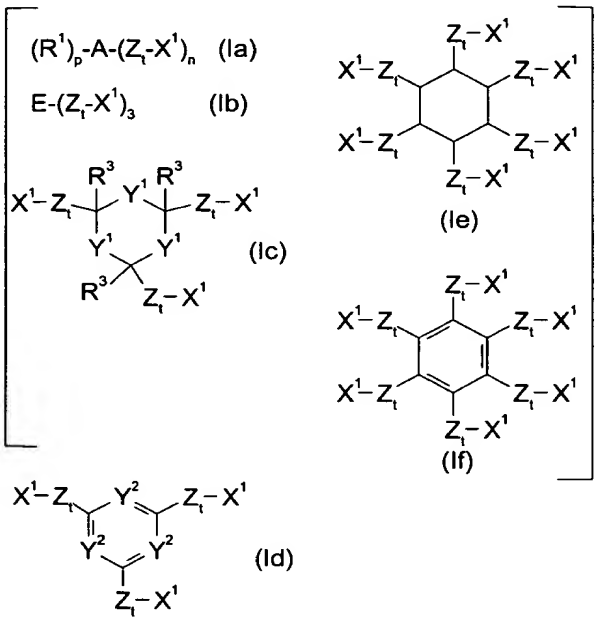
(IId)

31. (Amended twice) A liquid phase carrier (LPC), selected from the group consisting of [tetrakis{6,9-diaza-13-(5'-O-(4,4'-dimethoxytriphenylmethyl)-2'-deoxythymidine-3'-O-yl)-2-oxa-5,10,13-trioxotridecyl}methane ((DMT-dT)$_4$-PE-LPC),] 1,3,5-tris{2,5-diaza-9-(5'-O-(4,4'-dimethoxytriphenyl-methyl)-2'-deoxythymidine-3'-O-yl)-1,6,9-trioxononyl}-benzene ((DMT-dT)$_3$-Aryl-LPC), [tetrakis(13-(2'-deoxythymidin-3'-O-yl)-6,9-diaza-2-oxa-5,10,13-trioxotridecyl)-methane (dT$_4$-PE-LPC),] and 1,3,5-tris(9-(2'-deoxythymidin-3'-O-yl)-2,5-diaza-1,6,9-trioxononyl)-benzene (dT$_3$-Aryl-LPC)[, tris-{3-aza-4,7-dioxo-7-(5'-O-(4,4'-dimethoxytriphenylmethyl)-2'-deoxythymidine-3'-O-yl)-heptyl}-amine ((DMT-dT)$_3$-

Amine-LPC) and tris(3-aza-7-(2'-deoxythymidine-3'-O-yl)-4,7-dioxoheptyl)-amine (dT_3-Amine-LPC)].

39. (Amended three times) A method of solution phase biopolymer synthesis, comprising the steps of:

(a) reacting an LPC with a first monomer N^1; wherein the LPC has [formulae (I)] <u>formula (Id)</u>:



wherein: [A is silicon; E is nitrogen or P(O); R^1 and R^3 are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; p is 0 or 1;] Z is any combination of 0-12 units selected from 1,4-phenylene and methylene, which units may be combined in any order; t is 0 or 1; X^1 is OH, SH, NH_2, COR^5 or $COOR^4$, where R^4 is selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl; and R^5 is halide, heteroaryl or pseudohalide; n is 3 or 4; [Y^1 is CH_2, NH, S or O;]

Y^2 is [selected from] CH [and N]; [R^1, R^3], X^1, [Y^1], Y^2 and Z are unsubstituted or substituted with one or more substituents each independently selected from Q; and Q is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonyl-alkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylamino-sulfonyl;

(b) separating and purifying the product of step (a);

(c) reacting the product of step (b) with a second monomer N^2, a dimer N^2-N^3 or a trimer N^2-N^3-N^4; and

(d) repeating steps (b) and (c) to produce an LPC-bound biopolymer having m monomers, where m is 3 to 100, wherein:

N^1, N^2, N^3...N^m are biopolymer monomers; and

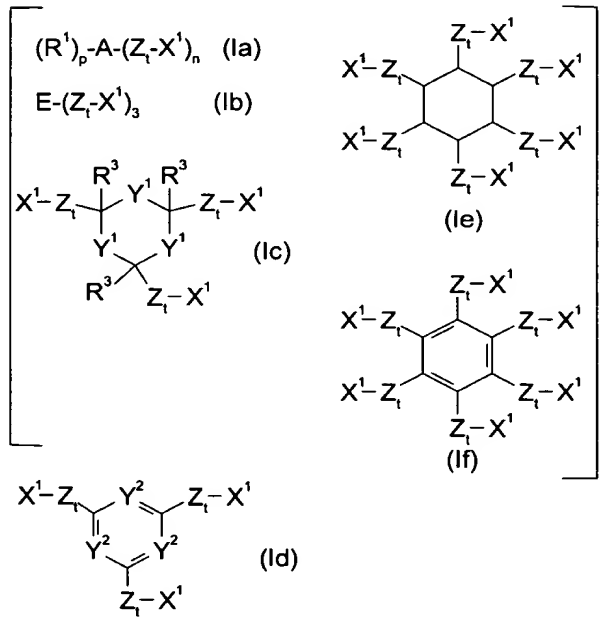
the dimers and trimers comprise the monomers.

40. (Amended twice) The method of claim 39, wherein the LPC is selected from the group consisting of [tetrakis{6,9-diaza-13-(5'-O-(4,4'-dimethoxytriphenylmethyl)-2'-deoxythymidine-3'-O-yl)-2-oxa-5,10,13-trioxotridecyl}methane ((DMT-dT)$_4$-PE-LPC),] 1,3,5-tris{2,5-diaza-9-(5'-O-(4,4'-dimethoxytriphenyl-methyl)-2'-deoxythymidine-3'-O-yl)-1,6,9-trioxononyl}-

benzene ((DMT-dT)$_3$-Aryl-LPC), [tetrakis(13-(2'-deoxythymidin-3'-O-yl)-6,9-diaza-2-oxa-5,10,13-trioxotridecyl)-methane (dT$_4$-PE-LPC)] and 1,3,5-tris(9-(2'-deoxythymidin-3'-O-yl)-2,5-diaza-1,6,9-trioxononyl)-benzene (dT$_3$-Aryl-LPC)[, tris-{3-aza-4,7-dioxo-7-(5'-O-(4,4'-dimethoxytriphenylmethyl)-2'-deoxythymidine-3'-O-yl]-heptyl}-amine ((DMT-dT)$_3$-Amine-LPC) and tris(3-aza-7-(2'-deoxythymidine-3'-O-yl)-4,7-dioxoheptyl)-amine (dT$_3$-Amine-LPC)].

48. (Amended Three times) A method of solution phase biopolymer synthesis, comprising the steps of:

(a) reacting an LPC with a first monomer N^1; wherein the LPC has [formulae (I)] formula (Id):



wherein: [A is silicon; E is nitrogen or P(O); R^1 and R^3 are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; p is 0 or 1;] Z is any combination of 0-12 units selected from 1,2-, 1,3- or 1,4-phenylene and [alkylene] methylene, which units may be combined in any order; t is 0 or 1; X^1 is OH, SH, NH_2, COR^5 or $COOR^4$, where

R^4 is selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl; and R^5 is halide, heteroaryl or pseudohalide; n is 3 or 4;[Y^1 is CH_2, NH, S or O;] Y^2 is [selected from] CH [and N]; [R^1, R^3,] X^1, [Y^1], Y^2 and Z are unsubstituted or substituted with one or more substituents each independently selected from Q; and Q is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl;

(b) separating and purifying the product of step (a);

(c) reacting the product of step (b) with a second monomer N^2, a dimer N^2-N^3 or a trimer N^2-N^3-N^4; and

(d) repeating steps (b) and (c) to produce an LPC-bound biopolymer having m monomers, where m is 3 to 100, wherein:

N^1, N^2, N^3...N^m are biopolymer monomers;

the dimers and trimers comprise the monomers; and

the protocol used in steps (c) and (d) to synthesize the biopolymer is the phosphoramidite protocol.